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Rhodium-Catalyzed Enantioselective Hydroamination of Alkynes with Indolines

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Abstract

The hydroamination of internal alkynes *via* tandem rhodium-catalysis gives branched *N*-allylic indolines with high regio- and enantioselectivity. An acid-switch provides access to the linear isomer in preference to the branched isomer by an isomerization mechanism. Mechanistic studies suggest formation of an allene intermediate, which undergoes hydroamination to generate allylic amines instead of the enamine or imine products typically observed in alkyne hydroaminations.

Constructing C–N bonds with high regio- and enantiocontrol represents an important challenge given the occurrence of amines in agrochemicals, fine-chemicals, and pharmaceuticals. Transition-metal catalysis has enabled the coupling of amines with allylic-electrophiles to provide either the branched or linear isomers (Figure 1a).[1] The hydroamination of alkynes has emerged as an attractive approach for C–N bond formation because of its high atom economy.[2] The majority of metal-catalysts investigated provide enamine or imine products (Figure 1b). In contrast, Yamamoto demonstrated a Pd-catalyzed hydroamination of internal alkynes to yield allylic amines, with preference for the linear isomers (Figure 1c).[3] While a promising approach, no intermolecular variants have been shown to access the corresponding branched isomers. Herein, we demonstrate a Rh-catalyzed alkyne hydroamination[4] that allows access to either the branched or linear isomers, with high regiocontrol by choice of carboxylic acid additive (Figure 1d). This communication showcases the first enantioselective intermolecular hydroamination of alkynes.

Late transition-metal hydrides (e.g., Ru, Rh, Ir, Pd) are known to convert alkynes to π-allyl metal intermediates. Since Yamamoto's report,[3] Ishii,[5] Krische,[6] and our group[7] have used metal-hydride catalysis to couple internal alkynes with alcohols or aldehydes to generate C–C bonds. The Breit group pioneered the use of terminal alkynes to form allylrhodium intermediates that undergo C–O and C–S bond formations.[8] Encouraged by this emerging

ASSOCIATED CONTENT
Supporting Information
Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

concept, we focused on the functionalization of alkynes to generate C–N bonds with both regio- and enantiocontrol.

To test our hypothesis, we chose the coupling of indoline **1a** and 1-phenyl-1-propyne **2a** as model substrates (Table 1). Commercially available metal hydride complexes (e.g., RuHCl(CO)(PPh$_3$)$_3$, RhH(CO)(PPh$_3$)$_3$, or IrH(CO)(PPh$_3$)$_3$) did not promote hydroamination. In contrast, a mix of [Rh(COE)$_2$Cl]$_2$/**L1** and benzoic acid[8] afforded the desired branched indoline **3aa** in trace amounts (4% yield, entry 1).[9] More electron rich and bulky ligands **L2** and **L3** improved reactivity and gave high regioselectivities (**3aa/4aa**) and moderate enantioselectivities (47-55% ee, entries 2-3). Among the bidentate phosphines bearing point chirality that we studied, (*S,S*)-BDPP **L6** gave the most promising regio- and enantioselectivity (87% ee, entry 6). We assume this ligand shows enhanced reactivity and selectivity due to its ability to promote isomerization and hydroamination in parallel. In the absence of acid, no hydroamination was observed. By investigating other acid additives, we found higher enantioselectivity using *m*-xylylic acid (90% ee, entry 7).

With this protocol in hand, we explored the hydroamination of alkyne **2a** with various amines **1** (Table 2). Good yields (72% and 81%) and high enantioselectivities (90% ee) were obtained using indolines with varying substituents at the 4-position (**3ba** and **3ca**). Substrates bearing fluoro, chloro, and bromo at the 5-position were transformed into allylic amines with similar efficiency (**3da-3fa**). A slight decrease in enantioselectivity was observed with indolines containing electron-donating substituents at the 5- or 6-position (**3ga** *vs* **3ha**, **3ia**). In contrast, an aliphatic amine, such as morpholine, showed poor reactivity under this protocol (8% yield, **3ja**). An improved yield (47%, **3ja**) could be obtained by using more *m*-xylylic acid (50 mol%). Aniline **1k** was coupled with alkyne **2a** in good selectivity (>20:1 b/l, 76% ee, **3ka**) without bisallylation. In all cases, we observed excellent regioselectivity for the branched isomers in preference to the linear isomers.

Next, we examined the scope of alkynes (Table 3). The use of electron rich 1-aryl-1-propynes **2b-c** gave branched allylic amines in >20:1 regioselectivities, 70-73% yields, and 82-91% ee (entries 1-2). Although a decrease in regioselectivity (from 20:1 to 3:1) was observed with electron deficient alkynes **2d-g**, high enantioselectivities (86-92%) were still achieved (entries 3-6). The coupling of indoline with *meta*-substituted 1-phenyl-1-propynes **2h-j** gave a slight increase in enantioselectivity (90-94%, entries 7-9). This protocol tolerated a heterocycle-substituted alkyne **2k** (80% yield, entry 10). However, low reactivity (15% yield) and selectivity (27% ee) were obtained using the internal alkyne **2l** bearing an aliphatic group (entry 11). The hydroamination of terminal alkyne **2m** gave the same product as that of **2a**, with similar regioselectivity and enantioselectivity but lower reactivity (entry 12). Poor enantioselectivity (7%) was observed in the hydroamination of 1-octyne **2n** (entry 13).[10] These results suggest that an aromatic substituent on alkyne **2** is critical for high yield and selectivity.

A one-pot protocol was developed, using Rh-catalyzed asymmetric hydroamination and subsequent oxidative dehydroaromatization of indolines **3**, to provide facile access to *N*-allylic indoles[11] **5aa** (90% ee) and **5ba** (85% ee) (eq. 1). The absolute configuration of **5aa** was determined to be (*S*) by comparison of its optical rotation with literature data.[11c-d,12]
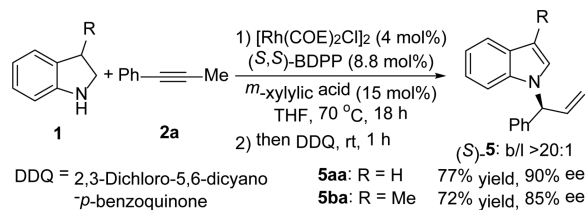
$$(1)$$

During our optimization studies, we found that using phthalic acid (benzene-1,2-dicarboxylic acid)[13] instead of *m*-xylylic acid gave linear allylic amines with high regioselectivity (>20:1). A number of amines are suitable coupling partners (**4aa, 4la-4oa**). By tuning the stoichiometry of aniline **1k** (PhNH$_2$) and alkyne **2a**, either monoallylated product **4ka** or bisallylated product **4ka'** could be formed exclusively. This protocol can be applied to 1-phenyl-1-butyne **2n**, which bears an ethyl group, to generate allylic amine **4ao**.

On the basis of literature[1,8] and our observations, we propose a pathway involving tandem Rh-catalysis (Figure 2). The oxidative addition of carboxylic acid with Rh(I) precursor generates a rhodium (III)-hydride species. The insertion of alkyne **2a** into the Rh(III)–H gives Rh-vinyl intermediate **A**, which subsequently undergoes β-hydride elimination to form intermediate allene **6** and regenerate the Rh(III)–H species. Reinsertion of the terminal allene **6** into Rh(III)–H yields a chiral π-allyl rhodium complex **B**. Two competing pathways can be considered for formation of product **3**.[14] For path A, a ligand exchange of amine **1** with the benzoate (X) on complex **B** will give π-allyl rhodium species **C**, which can undergo reductive elimination to yield allylic amine **3**. In path B, amine **1** undergoes nucleophilic attack at the carbon center to deliver allylic amine **3**.

To support the proposed allene intermediate, phenylallene **6** was prepared and then subjected to coupling with indoline **1a** under otherwise standard conditions (eq. 2).[15] Only a trace amount of the expected allylic amine was generated using a high concentration (~1.20 M) of allene **6**. However, the allene was transformed into the expected allylic amines when using a lower concentration (~0.16 M). Our results support the feasibility of allene **6** as the intermediate and suggest that high concentrations of allene inhibit catalysis. Using alkynes as allene surrogates can enable transformations that would be sluggish with allene precursors.[6a,7]
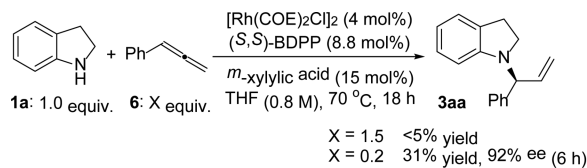
$$(2)$$

When the hydroamination was performed with deuterated alkyne **2a**-*d*$_3$, the deuterium label was scrambled into the α-, β- and γ-positions of amine **3aa**-*d*$_n$ (eq. 3). The observed

incorporation of hydrogen at the γ-position of amine **3aa**-d_n indicates the reversibility of β-hydride elimination during allene formation.
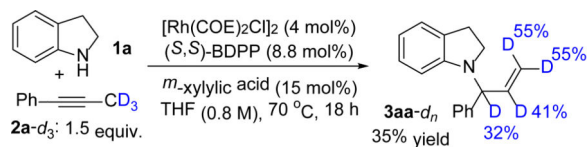
(3)

To better understand the regioselective switch (Table 2 *vs* 4), we isolated and subjected racemic **3aa** to various conditions (Figure 3). No isomerization was observed in the absence of either Rh or acid. However, the branched isomer **3aa** underwent isomerization to the linear product **4aa** faster in the presence of a more acidic additive (e.g., *m*-xylylic *vs* phthalic acid). Thus, the branched isomer is the kinetic product, which can be generated in high yield using *m*-xylylic acid. In contrast, our phthalic acid protocol generates linear products by a thermodynamically controlled isomerization. Indeed, when we monitored the reaction profile for our linear-selective hydroamination, we observed formation of the branched isomer at early time points followed by its conversion to the linear. Yudin observed a related isomerization of allylic amines under Pd-catalysis, whereby the kinetic (branched) product was favored by addition of DBU.[16]

Our Rh-catalyzed hydroamination provides an atom economical synthesis of allylic amines that complements traditional allylic aminations, which require the use of leaving groups. Mechanistic studies support the *in situ* formation of an allene which undergoes hydroamination to provide allylic amines, rather than the typically observed products of alkyne hydroamination (e.g., imines and enamines). Phthalic acid promotes isomerization of the kinetically favored isomers to yield the more stable linear isomers. Future studies will focus on catalyst design to extend substrate scope and develop other variants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

REFERENCES

1.
For selected reviews on allylic substitutions, see: Tsuji J, Minami I. Acc. Chem. Res. 1987; 20:140.Trost BM, Van Vranken DL. Chem. Rev. 1996; 96:395. [PubMed: 11848758] Johannsen M, Jørgensen KA. Chem. Rev. 1998; 98:1689. [PubMed: 11848944] Trost BM, Crawley ML. Chem. Rev. 2003; 103:2921. [PubMed: 12914486] Helmchen G, Dahnz A, Dübon P, Schelwies M, Weihofen R. Chem. Commun. 2007:675.Falciola CA, Alexakis A. Eur. J. Org. Chem. 2008:3765.Lu Z, Ma S. Angew. Chem. Int. Ed. 2008; 47:258.Trost BM, Zhang T, Sieber JD. Chem. Sci. 2010;

1:427.Hartwig JF, Stanley LM. Acc. Chem. Res. 2010; 43:1461. [PubMed: 20873839] Poli G, Prestat G, Liron F, Kammerer-Pentier C. Top. Organomet. Chem. 2012; 38:1.Milhau L, Guiry PJ. Top. Organomet. Chem. 2012; 38:95.Liu W-B, Xia J-B, You S-L. Top. Organomet. Chem. 2012; 38:155.Begouin J-M, Klein JEMN, Weickmann D, Plietker B. Top. Organomet. Chem. 2012; 38:269.

2.

For selected reviews on hydroaminations, see: Müller TE, Beller M. Chem. Rev. 1998; 98:675. [PubMed: 11848912] Nobis M, Driessen-Hölscher B. Angew. Chem. Int. Ed. 2001; 40:3983.Pohlki F, Doye S. Chem. Soc. Rev. 2003; 32:104. [PubMed: 12683107] Alonso F, Beletskaya IP, Yus M. Chem. Rev. 2004; 104:3079. [PubMed: 15186189] Odom AL. Dalton Trans. 2005:225. [PubMed: 15616708] Severin R, Doye S. Chem. Soc. Rev. 2007; 36:1407. [PubMed: 17660874] Müller TE, Hultzsch KC, Yus M, Foubelo F, Tada M. Chem. Rev. 2008; 108:3795. [PubMed: 18729420] Hannedouche J, Schulz E. Chem. Eur. J. 2013; 19:4972. [PubMed: 23450637] Reznichenko AL, Nawara-Hultzsch AJ, Hultzsch KC. Top. Curr. Chem. 2014; 343:191. [PubMed: 24276959] Huang L, Arndt M, Gooβen K, Heydt H, Gooβen LJ. Chem. Rev. 2015; 115:2596. [PubMed: 25721762]

3. a Kadota I, Shibuya A, Lutete LM, Yamamoto Y. J. Org. Chem. 1999; 64:4570. [PubMed: 11674520] b Lutete LM, Kadota I, Yamamoto Y. J. Am. Chem. Soc. 2004; 126:1622. [PubMed: 14871079] c Patil NT, Lutete LM, Wu H, Pahadi NK, Gridnev ID, Yamamoto Y. J. Org. Chem. 2006; 71:4270. [PubMed: 16709071] d Patil NT, Wu H, Yamamoto Y. J. Org. Chem. 2007; 72:6577. [PubMed: 17636960] e Narsireddy M, Yamamoto Y. J. Org. Chem. 2008; 73:9698. [PubMed: 18855453]

4.

For the synthesis of enamines or imines by Rh-catalyzed alkyne hydroaminations, see: Hartung CG, Tillack A, Trauthwein H, Beller M. J. Org. Chem. 2001; 66:6339. [PubMed: 11559184] Fukumoto Y, Asai H, Shimizu M, Chatani N. J. Am. Chem. Soc. 2007; 129:13792. [PubMed: 17949090] Alonso-Moreno C, Carrillo-Hermosilla F, Romero-Fernández J, Rodríguez AM, Otero A, Antinolo A. Adv. Synth. Catal. 2009; 351:881.Sakai K, Kochi T, Kakiuchi F. Org. Lett. 2011; 13:3928. [PubMed: 21699251] Kumaran E, Leong WK. Organometallics. 2012; 31:1068.

5. a Obora Y, Hatanaka S, Ishii Y. Org. Lett. 2009; 11:3510. [PubMed: 19719194] b Hatanaka S, Obora Y, Ishii Y. Chem. Eur. J. 2010; 16:1883. [PubMed: 20029924]

6. a Park BY, Nguyen KD, Chaulagain MR, Komanduri V, Krische MJ. J. Am. Chem. Soc. 2014; 136:11902. [PubMed: 25075434] b Liang T, Nguyen KD, Zhang W, Krische MJ. J. Am. Chem. Soc. 2015; 137:3161. [PubMed: 25734220]

7. Chen Q-A, Cruz FA, Dong VM. J. Am. Chem. Soc. 2015; 137:3157. [PubMed: 25608143]

8. a Lumbroso A, Koschker P, Vautravers NR, Breit B. J. Am. Chem. Soc. 2011; 133:2386. [PubMed: 21291216] b Lumbroso A, Abermil N, Breit B. Chem. Sci. 2012; 3:789.c Gellrich U, Meiβner A, Steffani A, Kähny M, Drexler H-J, Heller D, Plattner DA, Breit B. J. Am. Chem. Soc. 2014; 136:1097. [PubMed: 24377792] d Xu K, Khakyzadeh V, Bury T, Breit B. J. Am. Chem. Soc. 2014; 136:16124. [PubMed: 25365339] e Koschker P, Kähny M, Breit B. J. Am. Chem. Soc. 2015; 137:3131. [PubMed: 25667963]

9.

For the synthesis of 3aa by Ir-catalyzed allylic amination, see: Shu CT, Leitner A, Hartwig JF. Angew. Chem. Int. Ed. 2004; 43:4797.

10.

For alkyne 2l, no decomposition of starting materials was observed after 18 h. For alkyne 2m, competitive alkyne decomposition (dimerization and trimerization) was observed by GC/MS. The use of other internal alkynes (e.g., 1-phenyl-1-butyne) alkynes gave trace amounts of product.

11.

For the asymmetric synthesis of N-allylic indoles, see: Stanley LM, Hartwig JF. Angew. Chem. Int. Ed. 2009; 48:7841.Cui H-L, Feng X, Peng J, Lei J, Jiang K, Chen Y-C. Angew. Chem. Int. Ed. 2009; 48:5737.Liu W-B, Zhang X, Dai L-X, You S-L. Angew. Chem. Int. Ed. 2012; 51:5183.Ye K-Y, Dai L-X, You S-L. Chem. Eur. J. 2014; 20:3040. [PubMed: 24677302] Chen L-Y, Yu X-Y, Chen J-R, Feng B, Zhang H, Qi Y-H, Xiao W-J. Org. Lett. 2015; 17:1381. [PubMed: 25738835]

12.

The absolute configurations of all other amines 3 were assigned by analogy.

13.

Other acids (TFA, tartaric acid, malonic acid) which have pKa's from -0.3 to 3 promote the linear selective hydroamination. Phthalic is the optimal acid with respect to substrate generality.

14.

For Rh-catalyzed enantiospecific or enantioselective allylic aminations, see: Evans PA, Robinson JE, Nelson JD. J. Am. Chem. Soc. 1999; 121:6761.Evans PA, Clizbe EA. J. Am. Chem. Soc. 2009; 131:8722. [PubMed: 19499919] Vrieze DC, Hoge GS, Hoerter PZ, Van Haitsma JT, Samas BM. Org. Lett. 2009; 11:3140. [PubMed: 19527001] Arnold JS, Nguyen HM. J. Am. Chem. Soc. 2012; 134:8380. [PubMed: 22563701] Arnold JS, Mwenda ET, Nguyen HM. Angew. Chem. Int. Ed. 2014; 53:3688.

15.

For Rh-catalyzed hydroamination of allenes, see: Cooke ML, Xu K, Breit B. Angew. Chem. Int. Ed. 2012; 51:10876.Li C, Kähny M, Breit B. Angew. Chem. Int. Ed. 2014; 53:13780.Xu K, Thieme N, Breit B. Angew. Chem. Int. Ed. 2014; 53:2162.Xu K, Thieme N, Breit B. Angew. Chem. Int. Ed. 2014; 53:7268.

16. a Watson IDG, Yudin AK. J. Am. Chem. Soc. 2005; 127:17516. [PubMed: 16332104] b Dubovyk I, Watson IDG, Yudin AK. J. Org. Chem. 2013; 78:1559. [PubMed: 23327430]
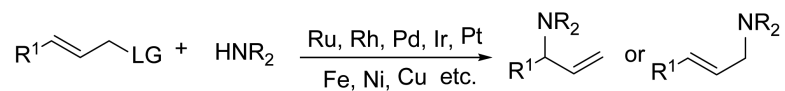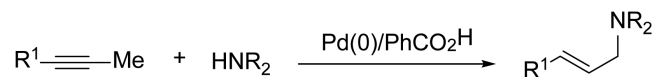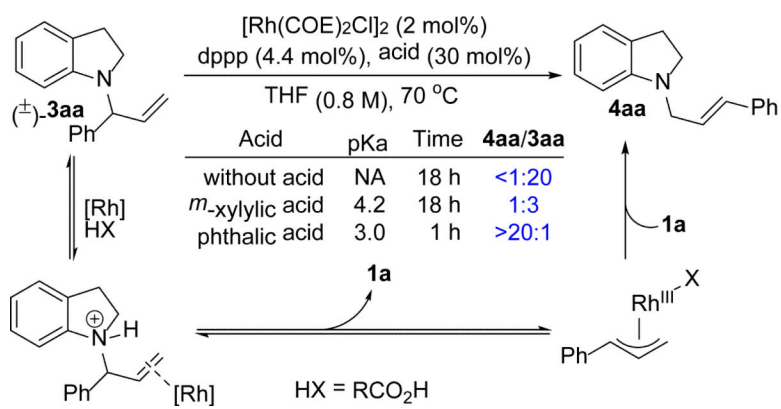
Figure 1.
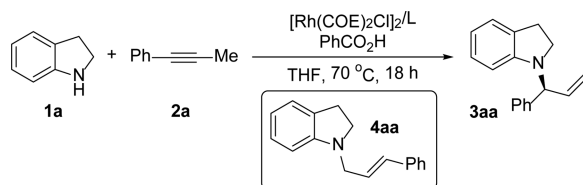Allylic Aminations versus Alkyne Hydroaminations
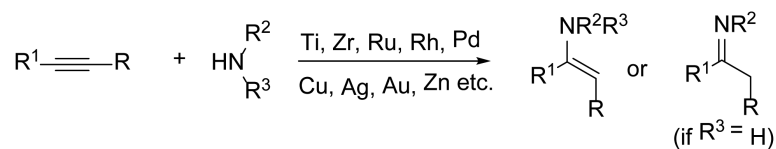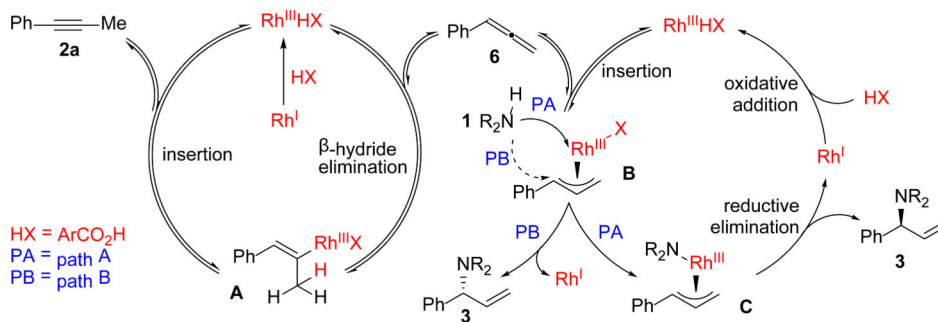
Figure 2.
Tandem Rh-Catalysis: Proposed Mechanism for Hydroamination of Alkynes

Figure 3.
Acid-Promoted Isomerization Study

Table 1

Ligand Effects on Hydroamination of Alkyne[a]

entry	ligand	3aa/4aa[b]	yield of 3aa (%)[b]	ee (%)[c]
1	**L1**	>20:1	4	ND
2	**L2**	19:1	18	55
3	**L3**	>20:1	64	47
4	**L4**	5:1	2	ND
5	**L5**	4:1	57	47
6	**L6**	>20:1	62	87
7[d]	**L6**	>20:1	80[e]	90

[a] **1a** (0.10 mmol), **2a** (0.12 mmol), [Rh(COE)$_2$Cl]$_2$ (2 mol%), Ligand (4.4 mol%), PhCO$_2$H (30 mol%), THF (0.25 mL), 70 °C, 18 h.

[b] Determined by ^{1}H NMR or GC-FID with 1,3,5-trimethoxybenzene as the internal standard, ND = not determined.

[c] Determined by chiral SFC.

[d] **1a** (0.20 mmol), **2a** (0.30 mmol), [Rh(COE)$_2$Cl]$_2$ (4 mol%), (*S,S*)-BDPP (8.8 mol%), *m*-xylylic acid (15 mol%).
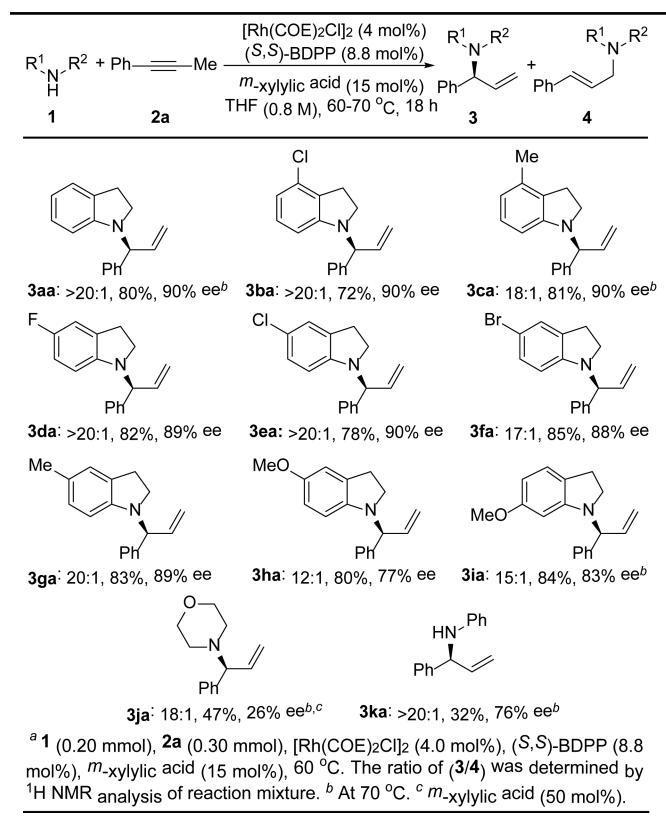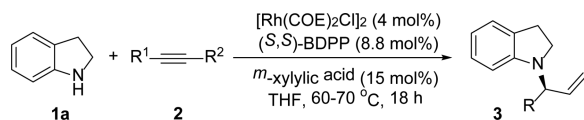
[e] Isolated yield.

Table 2

Branched-Selective Hydroamination with Various Amines[a]

[a] **1** (0.20 mmol), **2a** (0.30 mmol), [Rh(COE)₂Cl]₂ (4.0 mol%), (*S,S*)-BDPP (8.8 mol%), *m*-xylylic acid (15 mol%), 60 °C. The ratio of (**3/4**) was determined by ¹H NMR analysis of reaction mixture. [b] At 70 °C. [c] *m*-xylylic acid (50 mol%).

Table 3

Branched-Selective Hydroamination of Various Alkynes[a]

entry	R^1/R^2 in 2	3/4	yield (%)[b]	ee (%)[b]
1	4-MeC$_6$H$_4$/Me (2b)	>20:1	73	91 (3ab)
2[c]	4-MeOC$_6$H$_4$/Me (2c)	>20:1	70	82 (3ac)
3	4-FC$_6$H$_4$/Me (2d)	20:1	87	90 (3ad)
4	4-ClC$_6$H$_4$/Me (2e)	11:1	83	92 (3ae)
5	4-BrC$_6$H$_4$/Me (2f)	5:1	69	86 (3af)
6	4-CF$_3$C$_6$H$_4$/Me (2g)	3:1	70	91 (3ag)
7	3-MeC$_6$H$_4$/Me (2h)	>20:1	79	90 (3ah)
8	3-FC$_6$H$_4$/Me (2i)	11:1	82	94 (3ai)
9	3-ClC$_6$H$_4$/Me (2j)	8:1	81	93 (3aj)
10	3-Thienyl/Me (2k)	7:1	80	65 (3ak)
11[c]	Cy/Me (2l)	2:1	15	27 (3al)
12[c]	Bn/H (2m)	19:1	37	89 (3aa)
13[c]	n-C$_6$H$_{13}$/H (2n)	7:1	29	7 (3an)

[a]1a (0.20 mmol), 2 (0.30 mmol), [Rh(COE)$_2$Cl]$_2$ (4.0 mol%), (S,S)-BDPP (8.8 mol%), m-xylylic acid (15 mol%), THF (0.25 mL), 60 °C. The ratio of 3/4 was determined by ^{1}H NMR analysis of reaction mixture.

[b]Isolated yield and ee of 3.

[c]At 70 °C.

Table 4

Linear-Selective Hydroamination of Alkynes[a]

4aa: 91% yield

4la: 99% yield

4ma: 95% yield

4na: 85% yield

4oa: 77% yield

4ka: 55% yield
(with 1k/2a 3:2)

4ka': 70% yield
(with 1k/2a 2:5)

4ao: 79% yield